An asymmetric synthesis of ADDA and ADDA-glycine dipeptide using the β-lactam synthon method

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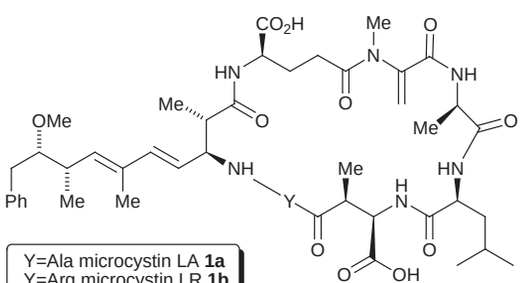
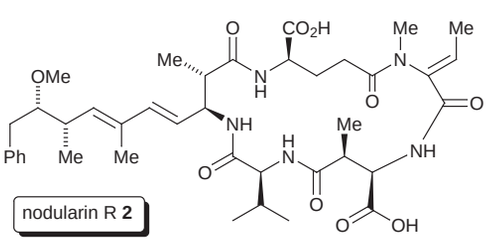
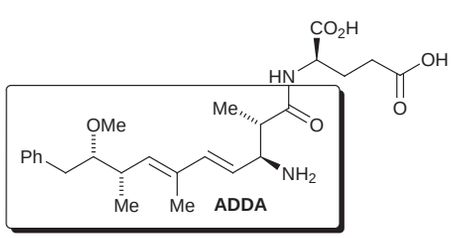
The paper describes the synthesis of the *N*-Boc lactam **4** and demonstrates that it is an important intermediate in the synthesis of dipeptide **5** (X = H, *n* = 0, R = Me), an analogue of the ADDA-Glu dipeptide **3**. In addition we have described a mild method for the preparation of the amino acid salt ADDA·HCl and provided synthetic methods and full characterisation for the previously 'elusive' free amino acid ADDA.

Introduction

The microcystin (*e.g.*, microcystin LA **1a** and LR **1b**) and nodularin (*e.g.*, nodularin R **2**) families of cyclic peptides are potent hepatotoxins.[2] In order to probe their structure-activity relationship we wanted to prepare analogues of the ADDA-glutamic acid dipeptide **3**, a common feature of these peptides. As *N*-Boc







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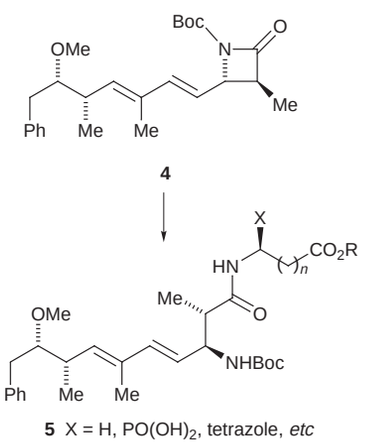
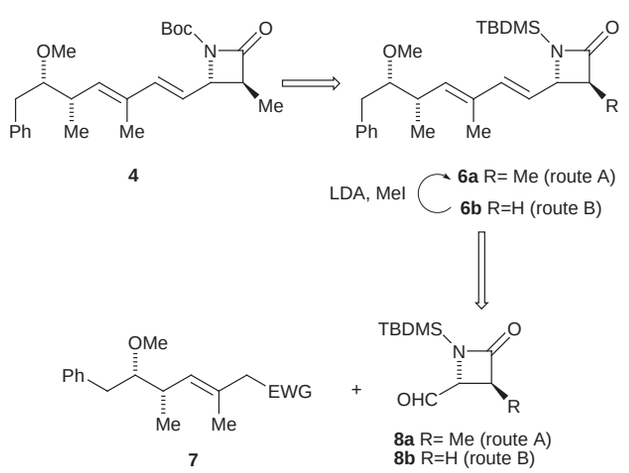
β-lactams have recently been shown to give dipeptides on reaction with amino esters,[3] we identified the *N*-Boc β-lactam **4** as a versatile intermediate to achieve this goal (Scheme 1). This paper describes the synthesis of the β-lactam **4**, its reaction with glycine methyl ester to form an analogue **5** (X = H, *n* = 0, R = Me) of the dipeptide **3**, and in addition provides the first full characterisation of the parent amino acid, ADDA.



Scheme 1



Scheme 2

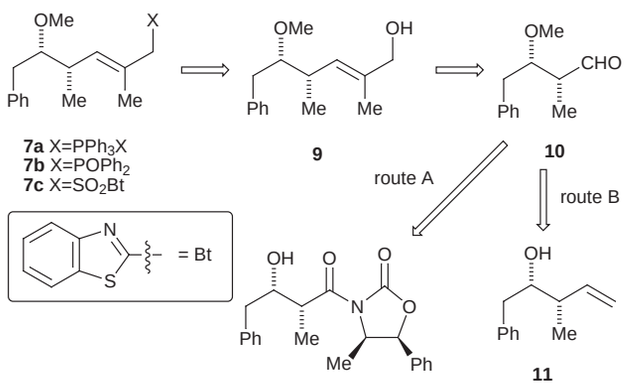
The retrosynthesis of β-lactam **4** is outlined in Scheme 2. The β-lactam ring provides both a means for the preparation of the required peptide bond of compound **5** and a scaffold for the introduction of the *anti*-α-methyl-β-amino acid motif within the ADDA amino acid residue as C-4-substituted β-lactams are known to undergo enolate alkylations at C-3 to give predominantly the *trans*-disubstituted products.[4] Due to the high reactivity of *N*-Boc lactams,[3,5] we considered the *N*-Boc lactam **4** too unstable to participate in the required enolate alkylation chem-

istry. However, as *N*-TBDMS β-lactams are known to undergo enolate alkylations and the N–TBDMS bond is easily cleaved,[4,6] our initial target became lactam **6a** or **6b**. We chose to assemble the diene fragment within lactam **6a** or **6b** through condensation of an allylic coupling partner **7** and β-lactam aldehyde **8a** or **8b**.[6b] While the introduction of the C-2 methyl group could take place either before (route A, Scheme 2) or after (route B, Scheme 2) the diene assembly, the more convergent route A became the focus of our initial investigations, the result of which are described here.[7]

Results and discussion

Synthesis of allylic coupling partners 7a–c

The synthesis of the phosphonium salt **7a** has been described previously using the general retrosynthesis illustrated in Scheme 3, route A and applied to the synthesis of ADDA derivatives.[8a–c,f] These literature reactions using the phosphonium salt **7a** give approximately a 1:1 mixture of *E* and *Z* isomers, so while the phosphonium salt **7a** was to be assessed in this work, we were also interested in investigating the coupling using the phosphine oxide **7b**[9] and the benzothiazole sulfone **7c**[10],† due to their efficacy in the synthesis of related *E*,*E*-dienes.[11,12] The common intermediate for compounds **7a**–**c** is the allylic alcohol **9**, prepared from the aldehyde **10** by a Wittig reaction/reduction procedure. Of the two standard methods for the stereospecific preparation of aldehyde **10**, we chose the Brown crotylation methodology[13] (Scheme 3, route B) as

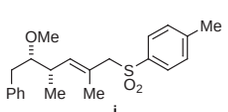


Scheme 3

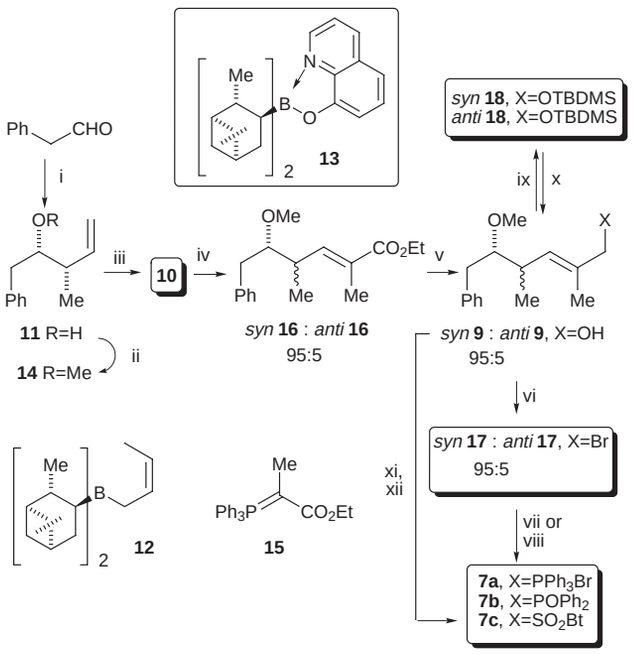
opposed to the previously described Evans methodology[8c,f,14] due to the fact that (i) the terminal alkene is a more convenient source of the aldehyde than an Evan's oxazolidone, (ii) the methyl ether could be introduced through standard Williamson synthesis without competing retro-aldol fragmentation, and (iii) the intermediates could be purified by distillation, allowing the synthesis of compounds **7a**–**c** to be more conveniently carried out on a large scale.

Reaction of phenylacetaldehyde with the borane **12**[13] and work-up with 8-hydroxyquinoline[13c] gave the *syn*-homoallylic alcohol **11** (Scheme 4). ^{1}H NMR analysis confirmed both the diastereo- and enantioselectivity for this reaction to be >95%.[15] The work-up procedure permitted the pinene-derived chiral auxiliary to be removed as the solid complex **13**, allowing the alcohol **11** to be isolated in the filtrate of the work-up solution. The alcohol **11** was directly methylated to give the alkene

† The "traditional" sulfone **i** has been applied to the synthesis of ADDA derivatives (ref. 8*d*,*e*).



i



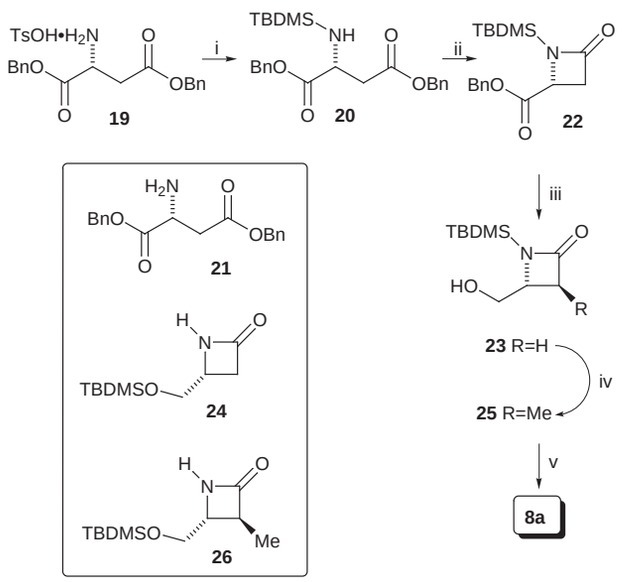
Scheme 4 *Reagents*: (i) **12**; (ii) NaH, MeI; (iii) O_3, PPh_3; (v) **15**; (v) $LiAlH_4$; (vi) CBr_4, PPh_3; (vii) PPh_3, *anti* **7a**:*syn* **7b**, 95:5; (viii) $EtOPPh_2$, recryst., *anti* **7b**:*syn* **7b**, 100:0; (ix) TBDMSCl; (x) MeOH, acid; (xi) BtSH, DEAD, PPh_3; (xii) Oxone or H_2O_2, *anti* **7c**:*syn* **7c**, 100:0.

14. The efficacy of the Brown crotylation combined with the 8-hydroxyquinoline work-up and simple short-path distillation of the alkene **14** allowed the conversion of phenylacetaldehyde to the alkene **14** to be conducted on a 80 mmol scale in 85–90% yield. Ozonolysis of the alkene **14** followed by reductive work-up gave the aldehyde **10**[8b–e,g] which was treated without purification with the Wittig reagent **15** to give, after short-path distillation, the αβ-unsaturated ester **16** in 80–85% yield. ^{1}H NMR analysis indicated that the *E*:*Z* ratio was >20:1, but that the expected product ***syn*-16**[8b–e] was contaminated with ~5% of the C-4 epimer ***anti*-16**, which could not be removed by chromatography. A similar level of epimerisation has been reported previously for this reaction.[8b–e] Reaction of the aldehyde **10** with the Horner–Wadsworth–Emmons reagent, triethyl 2-phosphonopropionate, favoured the formation of ***Z*-16** (ratio of ***Z*-16**:***E*-16**, 60:40) in addition to inducing a similar level (~5%) of epimerisation. $LiAlH_4$ reduction[8d,e] of the mixture of esters ***syn*-16** and ***anti*-16** (ratio 95:5) followed by work-up with $Na_2SO_4{\cdot}10H_2O$ gave a mixture of alcohols ***syn*-9**[8a,f] and ***anti*-9** in quantitative yield. Conversion of this mixture of alcohols to the bromides ***syn*-17**[8b,c,f] and ***anti*-17** (65–70% yield) and reaction with PPh_3 gave the phosphonium salts ***syn*-7a** and ***anti*-7a**.[8a–c,f] As attempted recrystallisation of this material was unsuccessful, the phosphonium salt was used in subsequent reactions as the 95:5 mixture of *syn* and *anti* diastereoisomers. Alternatively, reaction of the bromides ***syn*-17** and ***anti*-17** with $EtOPPh_2$ gave the crude phosphine oxide **7b**. Recrystallisation gave diastereoisomerically pure phosphine oxide ***syn*-7b** in 70–75% yield. The allylic alcohol ***syn*-9** could be separated from stereoisomer ***anti*-9** after conversion to the TBDMS ethers ***syn*-18** and ***anti*-18**.[8e] While the R_f difference between isomers ***syn*-18** and ***anti*-18** was small, significant quantities of ***syn*-18** could be purified and converted to alcohol ***syn*-9**. Mitsunobu reaction of alcohol ***syn*-9** and 2-mercaptobenzothiazole (BtSH) followed by oxidation of the intermediate sulfide with either Oxone®[16] or molybdenum-catalysed H_2O_2[12] gave the sulfone ***syn*-7c** in 70–75% yield for the two steps. Direct recrystallisation of the sulfone **7c** prepared from the mixture of alcohols ***syn*-9** and ***anti*-9** did not remove all of the unwanted *anti*-isomer, although the recrystallisation procedure has not been repeated after a

seed crystal of diastereoisomerically pure sulfone ***syn*-7c** was prepared from alcohol ***syn*-9**.

Synthesis of β-lactam aldehyde 8a

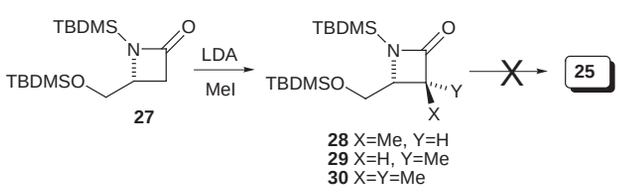
The synthesis of aldehyde **8a** is shown in Scheme 5. The



Scheme 5 *Reagents*: (i) TBDMSCl, NEt_3; (ii) ^{t}BuMgCl; (iii) $NaBH_4$, LiBr; (iv) base, MeI (see text); (v) oxidation (see text).

toluene-*p*-sulfonic acid salt of dibenzyl-D-aspartate[17] **19** was treated with TBDMSCl in the presence of 2 equivalents of Et_3N under anhydrous conditions to give dibenzyl *N*-TBDMS-D-aspartate **20** in >90% yield. Compound **20** is sufficiently stable in solution to allow the liberated $Et_3N{\cdot}HCl$ to be removed by aqueous work-up; however, the neat liquid was relatively unstable and prolonged storage or extensive manipulation led to decomposition to give the free amine **21** and therefore it was used in further reactions immediately. ***ent*-20** has previously been prepared in a two-step process from the salt ***ent*-19** by liberation of the free amine ***ent*-21** and subsequent reaction with *N*-(*tert*-butyldimethylsilyl)-*N*-methyltrifluoroacetamide.[4f] Reaction of compound **20** with ^{t}BuMgCl proceeded smoothly to give the benzyl ester **22** in addition to an equivalent of benzyl alcohol.[4f] This crude material was treated with $NaBH_4$ in the presence of LiBr to give the alcohol **23** and a further equivalent of benzyl alcohol.[18] The alcohol **23** could be easily separated from the two equivalents of benzyl alcohol by silica gel chromatography. $Ca(BH_4)_2$ has been recommended[4n] for the reduction of ester (±)-**22** and related compounds in order to suppress migration of the TBDMS group from nitrogen to oxygen; however, use of the more convenient $NaBH_4$/LiBr reduction procedure led to only trace amounts of the lactam **24**,[4d] which was removed during chromatography. Reaction of 30–70 mmol of salt **19** delivered a 50–60% yield of alcohol **23** in a 3-step process requiring only the final product to be purified.‡ Reaction of the alcohol **23** with two equivalents of *n*-BuLi or LDA at −78 °C followed by addition of methyl iodide (1–3 equiv.) and quenching the reaction at −78 °C gave the *trans*-methylated lactam **25** stereospecifically as shown by the H-2–H-3 coupling of 2.4 Hz.[4g,n] As was expected no evidence was seen in the crude ^{1}H NMR spectrum of the *cis*-methylated lactam. Despite the reaction not proceeding beyond 70% conversion, the starting material could be easily separated from the product by chromatography and recycled. The isolated yield of the *trans*-methylated product **25** was 53–66% on a multigram scale. Varying the base [LDA, *n*-BuLi, lithium hexamethyldisilazide (LiHMDS)], the reaction time (both in the formation of the dianion and the MeI quench), the ratio of reagents or the addition of adjuncts (*e.g.* HMPA) all failed to improve the conversion beyond 70%. Attempts to perform the reaction at temperatures greater than −78 °C resulted in increasing amounts of the lactams **24** and **26** being isolated as a result of N ⟶ O silyl migration. At −30 °C the sole products of the alkylation were those derived from N ⟶ O silyl migration. Treatment of the alcohol **25** with either Dess–Martin's reagent[20] or under Swern[21] oxidation conditions gave the aldehyde **8a** in 90% yield. Due to the large molecular mass of Dess–Martin's reagent, the Swern protocol was preferred for larger scale oxidations. The aldehyde retained the *trans*-substitution of the methyl and formyl groups about the lactam ring ($J_{3,4}$ 2.8 Hz). The crude aldehyde **8a** obtained from the Swern oxidation procedure was of sufficient purity to be used immediately. Material of greater purity for characterisation was obtained by silica gel chromatography. In general, the aldehyde **8a** could be stored unchanged for weeks at −10 °C; however, as on one occasion some decomposition occurred, the aldehyde **8a** was used immediately it was prepared.

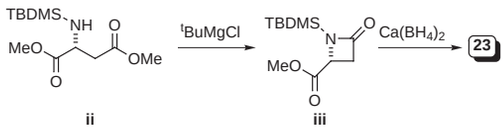
Thomas and Williams have reported[4k],§ that the methylation of the bis-TBDMS lactam **27** gave the mono-*trans*-alkylated lactam **28** in addition to ~10% of another compound, assumed to be the *cis*-lactam **29** (Scheme 6). Significantly, no bis-methyl-



Scheme 6

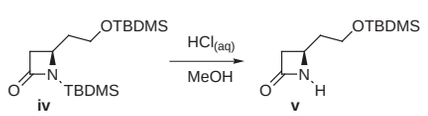
ated lactam **30** was detected. Indeed, lactam **28** was resistant to further alkylation using LDA as the base. In an effort to increase the amount of available alcohol **25** and hence aldehyde **8a**, we attempted the preparation of the methylated lactam **28** followed by selective removal of the *O*-TBDMS group.¶ Reaction of compound **27** with a large excess of LDA and MeI, under the conditions reported by Thomas and Williams, gave a quantitative yield of a mixture of the desired monomethyl lactam **28** and, surprisingly, the 3,3-dimethyl lactam **30** in a ratio of 3 : 1. A further reaction using a slight excess of LDA and MeI gave an improved ratio of products **28** : **30** of 9 : 1; however, no further improvements could be made and attempts to separate the two products by chromatography proved fruitless. Other workers have recently reported that dimethylation occurs during large-scale reactions of lactam ***ent*-27** with excess of LDA and MeI.[23] In addition, the *O*-TBDMS group could not be

‡ The *N*-silylation/cyclisation of the dimethyl ester **ii** to give the lactam **iii** was less efficient (~40% yield) when compared to the formation of lactam **22** from diester **20**. The conversion of **ii** to **iii** is described (no yield or characterisation) in a patent (ref. 19) outlining the synthesis of compound **27**. Curiously, reduction of ether **iii** to alcohol **23** with $NaBH_4$/LiBr gave a mixture of compounds **23** and **24**, whereas $Ca(BH_4)_2$ reduction of compound **iii** gave only alcohol **23** (see ref. 4*n*).



§ Thomas *et al*. performed the alkylation experiments on the opposite enantiomer, *i.e.*, lactam **27** derived from (*L*)-aspartic acid.

¶ A patent abstract (ref. 22) describes the selective *N*-desilylation of lactam **iv** (and other *N*,*O*-silyl lactams) to give compound **v**.

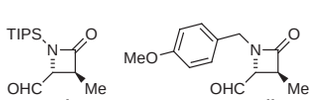


removed without some *N*-TBDMS cleavage so this route was abandoned.

Coupling of the allylic reagents 7a–c with β-lactam aldehyde 8a

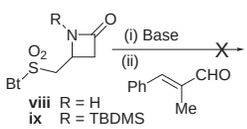
The couplings of **7a**–**c** and the aldehyde **8a** were studied extensively (Scheme 7). Deprotonation of the phosphonium salt **7a** with *n*-BuLi and addition of aldehyde **8a** in THF gave the lactam **6a** in 25% yield with an *E*:*Z* ratio of ~1:1. No attempt was made to optimise this reaction as we investigated more stereoselective processes. Deprotonation of the phosphine oxide **7b** with NaHMDS and addition of the aldehyde **8a** gave only the *E*-isomer; however, the yield of lactam **6a** was poor (10–15%). While some phosphine oxide **7b** could be recovered from these reactions, no aldehyde **8a** was detected in the crude reaction mixture even in reactions using >2 equivalents of aldehyde **8a**. The only isolated and identified product derived from aldehyde **8a** (other than diene **6a**) was *tert*-butyldimethylsilanol. The exact mode of decomposition of aldehyde **8a** remains unclear that this stage. Sodium seems to be the optimum counter-ion in this reaction, as replacement of NaHMDS by *n*-BuLi or KHMDS gave no identifiable products in the crude reaction mixture.‖ Curiously, inverse addition of the sodium salt of the phosphine oxide **7b** to a solution of aldehyde **8a** also gave no identifiable products. Replacing the phosphine oxide **7b** by the sulfone **7c** in the coupling reaction led to a significant increase in yield of coupled product. The yield and *E*:*Z* ratio of the diene from these reactions in THF varied with the nature of the base used to deprotonate the sulfone. To aid purification, the crude products were treated with KF to give the lactam **31** as the isolated product. Examination of the products isolated in this fashion indicated that KHMDS was the base of choice, delivering lactam **31** with a ~3:1 *E*:*Z* ratio in 40–45% yield over the two steps (coupling and desilylation) from sulfone **7c**. Reactions using NaHMDS were highly *E*-selective (*E*:*Z* ratio ~4:1); however, the yield was inferior (20–25%). Use of LiHMDS or LDA as base gave the poorest *E*:*Z* ratio of ~2:1. Reaction of the lactam **31** with $(Boc)_2O$ gave the *N*-Boc lactam **4** in 90–95% yield, which on reaction with glycine methyl ester in the presence of NaN_3 [3,24] gave the ADDA-Glu analogue dipeptide **5** (X = H, *n* = 0, R = Me) in 76% yield, significantly without epimerisation. The identity of the *N*-Boc lactam **4** was confirmed by conversion to *N*-Boc-ADDA [8c,f,h,i] using Greico's procedure.[25] Samples of the *N*-Boc lactam **4** containing mixtures of *E*- and *Z*-isomers could be separated by column chromatography either at this stage or after coupling to form the dipeptide **5**. This reaction confirms that the *N*-Boc lactam **4** is a useful intermediate for the synthesis of dipeptides **5**. Future work in this area includes further optimising the synthesis of the *N*-Boc lactam **4** and applying it to the synthesis of particular ADDA-containing dipeptides **5** as required for the synthesis of 'designer' microcystins and nodularins.

‖ Poor yields of coupled products were also obtained on reaction of phosphine oxide **7b** with aldehyde **8b**. While again only the desired *E*,*E*-diene was obtained, other products derived from substrate **8b** could not be isolated or identified. It should be noted that the reaction of aldehyde **8b** with CBr_4/Zn [6c] or Reformatsky,[6a] Peterson [4j] and stabilized Wittig [4k,l] reagents is reported to give the desired products in good yield. Reaction of the triisopropylsilyl (TIPS) lactam **vi** gave no coupled product and led to the destruction of substrate **vi**. Reaction of the *N*-*p*-methoxybenzyl (PMB) lactam **vii** with phosphine oxide **7b** gave an improved (30%) isolated yield of coupled product but in this case a ~1:1 mixture of inseparable *E* and *Z* diene isomers was obtained. In addition, oxidative deprotection with cerium(IV) ammonium nitrate (CAN) of this mixture led to decomposition.



vi **vii**

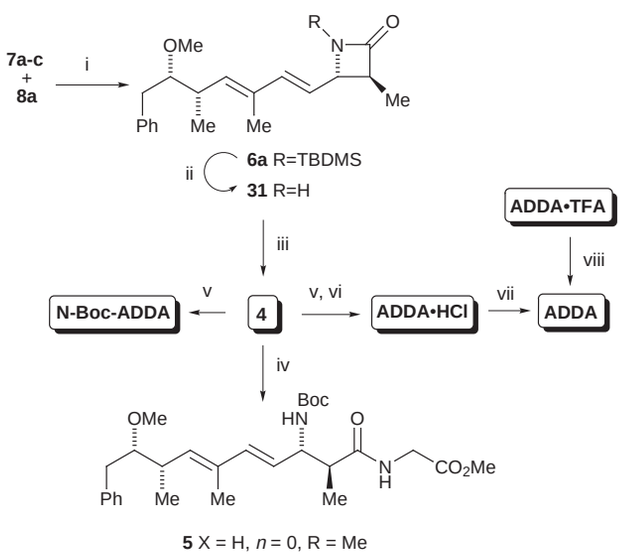
Reversing the polarity of the coupling process was briefly investigated. Attempted double deprotonation of compound (±)-**viii** or selective deprotonation of compound (±)-**ix** followed by addition of α-methylcinnamaldehyde gave no diene products.



viii R = H
ix R = TBDMS

Synthesis of ADDA

While there have been several papers over recent years [8] detailing synthetic approaches to various derivatives of ADDA, there is only one report [8a] of the preparation of ADDA although no experimental details were given and only an accurate mass measurement was reported. The lack of spectral data is in part due to the instability of ADDA under the conditions used to degrade microcystins and nodularins to their constituent amino acids.[8a] Full characterisation of a compound assigned as the free amino acid ADDA appeared in a recent thesis,[8e] but as the last purification step in this procedure was an extraction into dil. HCl, it appears this compound was the hydrochloride salt. In order to provide quantities of ADDA for a variety of applications, we were interested in developing methods for the conversion of our synthetic intermediates to ADDA. As acid hydrolysis has been shown to be an effective method for the conversion of β-lactams to β-amino acids,[3] we treated β-lactams **6** and **31** under a variety of acidic conditions, *e.g.* 6 M HCl in $CHCl_3$, 6 M HCl in MeOH, TMSCl in MEOH; however, no identifiable products were isolated. It appears that conditions vigorous enough to effect ring opening of the lactam also cause decomposition. The successful mild basic hydrolysis of the *N*-Boc lactam **4** to give *N*-Boc-ADDA described above led us to consider this intermediate as a precursor to ADDA (Scheme 7). To this end, *N*-Boc-ADDA was treated with HCl in



5 X = H, *n* = 0, R = Me

Scheme 7 *Reagents* (i) see text; (ii) KF, MeOH; (iii) $(Boc)_2O$; (iv) Gly(OMe), NaN_3; (v) LiOH; (vi) HCl, EtOAc; (vii) HCO_2NH_4 (aq); (viii) NH_3 (aq).

EtOAc [26] under mild conditions to give ADDA as its HCl salt in ~95% purity as assessed by HPLC analysis. The ^1H and ^{13}C NMR spectral data for this material agreed with those previously prepared and reported as being for the free amino acid ADDA.[8e] Purification of this material by HPLC (elution with 6:4 methanol–water containing ammonium formate) surprisingly gave the free amino acid ADDA. Apparently exchange of chloride ion for formate ion occurs on the column to give the formate salt of ADDA which, under high vacuum, decomposes to the free amino acid ADDA which was fully characterised. In

an alternative procedure, ADDA·TFA** was dissolved in aq. ammonia and the solution freeze dried to again give the free amino acid ADDA. In this case, ADDA is exchanged for ammonia to give ammonium trifluoroacetate which decomposes to trifluoroacetic acid and ammonia under high vacuum. Examination of the ^{1}H NMR spectra for the free amino acid ADDA showed that the resonances for H-2 and H-3 appear as broad pseudo-triplets with coupling of 7.2 and 8.4 Hz respectively. No other coupling is observed. In addition the chemical shifts for H-2 and H-3 were 0.2–0.4 ppm upfield of the respective peaks in the spectra for either ADDA·HCl or ADDA·TFA.

In conclusion, this work has described the synthesis of the *N*-Boc lactam **4** and demonstrated that it is an important intermediate in the synthesis of ADDA compound **5** (X = H, n = 0, R = Me), an analogue of the ADDA-Glu dipeptide **3**. In addition we have described a mild method for the preparation of the amino acid salt ADDA·HCl and provided synthetic methods and full characterisation for the previously 'elusive' free amino acid ADDA.

Experimental

General

Mps were determined using a Kyoma hotstage melting point apparatus and are uncorrected. Short-path distillations were performed using a Kugelrohr (bulb-to-bulb) distillation apparatus and temperatures are oven temperatures and serve only as a guide. Microanalysis were performed at the Chemistry Department, University of Otago, New Zealand. Optical rotations were measured using a JASCO DIP370 digital polarimeter in a cell of 1 dm in length at a wavelength of 598 nm (sodium D-line). Concentrations are expressed as c (g/100 ml). The temperature of all rotations was 22 ± 1 °C. $[a]_D$-Values are given in units of 10^{-1} deg cm^2 g^{-1}. IR spectra were recorded using a Perkin-Elmer 842 spectrometer (cm^{-1} scale) for samples as KBr disks of solids or as thin films of liquids between sodium chloride plates. ^{1}H NMR spectra were recorded at 200 MHz with a Bruker AC-200 spectrometer and refer to deuteriochloroform solutions with residual chloroform as the internal standard (δ_H 7.27) unless otherwise stated. *J*-Values are given in Hz. ^{13}C NMR spectra were recorded at 50 MHz with a Bruker AC-200 spectrometer and refer to deuteriochloroform solutions with residual chloroform as the internal standard (δ_C 77.0). ^{19}F NMR spectra were recorded at 188 MHz with a Bruker AC-200 spectrometer and refer to deuteriochloroform solutions with chemical shifts reported relative to CCl_3F (δ 0.00). Low-resolution CI MS and accurate mass determinations were recorded on a JOEL JMS-DX303 mass spectrometer. Atmospheric pressure chemical ionisation (APCI) MS were recorded on a FISONS Instrument VG Platform mass spectrometer. Analytical HPLC was performed on a LiChroCart C18 RP-HPLC column, 4 mm I.D. × 125 mm. All solvents were purified by literature procedures.[27] Unless otherwise stated, all reagents were purchased from Aldrich Chemical Company, Inc. Petroleum spirit refers to the fraction with distillation range 40–60 °C.

(3*S*,4*S*)-4-Methoxy-3-methyl-5-phenylpent-1-ene 14

(*Z*)-But-2-ene (23.2 ml, 250 mmol) was condensed into a solution of potassium *tert*-butoxide in THF (1 M; 91.6 ml, 91.6 mmol) at −78 °C. *n*-BuLi in hexanes (2.5 M; 18.3 ml, 91.6 mmol) was added dropwise while the internal temperature was maintained at below −70 °C. The reaction temperature was then allowed to reach −45 °C for 10 min and the mixture was recooled to −78 °C. (+)-β-Methoxydiisopinocampheylborane (32.9 g, 104 mmol) as a solution in Et_2O (60 ml) was added dropwise at −78 °C and the solution was stirred at this temperature for 45 min. Freshly distilled BF_3·OEt_2 (15.8 ml, 129 mmol) was added dropwise followed immediately by a solution of phenylacetaldehyde (10.0 g, 83.2 mmol) in Et_2O (40 ml) and the mixture was stirred at −78 °C overnight. The reaction was quenched with addition of anhydrous MeOH (16.8 ml, 415 mmol) and the mixture was concentrated *in vacuo* to leave a viscous oil. This residue was dissolved in anhydrous MeOH (150 ml), and the solution was cooled to 0 °C and treated with a solution of 8-hydroxyquinoline (15.1 g, 104 mmol) in MeOH (150 ml) to give a fluorescent yellow–green solution. The mixture was stirred overnight during which it reached ambient temperature and a fluorescent yellow–green solid had precipitated. Filtration through a short column of Florisil®, washing of the filter cake with small quantities of cold MeOH, and concentration of the filtrate *in vacuo* gave a fluorescent liquid. ^{1}H NMR analysis indicated the mixture contained (3*S*,4*S*)-4-hydroxy-3-methyl-5-phenylpent-1-ene **11** [^{1}H NMR: δ 1.13 (d, *J* 6.8, 3H), 2.27–2.40 (m, 1H), 2.61 (dd, *J* 9.3 and 13.7, 1H), 2.85 (dd, *J* 3.7 and 13.7, 1H), 3.68–3.77 (m, 1H), 5.08–5.10 (m, 1H), 5.14–5.19 (m, 1H), 5.76–5.96 (m, 1H), 7.19–7.37 (m, 5H) in addition to ~10% of borinate **13**. The enantiomeric excess of alcohol **11** was determined to be >95% after conversion to the corresponding (*R*)- and (*S*)-Mosher's esters [^{19}F NMR: δ −71.76 {major peak using (*R*)-Mosher's acid}, −72.01 {major peak using (*S*)-mosher's acid}].

This material was treated further without purification. NaH (60% in oil; 5.0 g, 124.8 mmol) was added in portions to a solution of the crude alcohol in THF (200 ml) containing methyl iodide (10.4 ml, 166.4 mmol) at 0 °C. The cooling bath was removed and the mixture was stirred until TLC analysis indicated the reaction was complete. The reaction mixture was cooled to 0 °C and treated cautiously with saturated aq. NH_4Cl (20 ml) and diluted with Et_2O (200 ml) and water (200 ml). The organic layer was separated, dried ($MgSO_4$), and filtered and the filtrate was concentrated *in vacuo* to give a yellow oil. Short-path distillation (150 °C at 0.1 mmHg) gave the *methyl ether* **14** (11.8 g, 75%) as a slightly yellow oil (Found: C, 81.8; H, 9.7. $C_{13}H_{18}O$ requires C, 82.1; H, 9.5%); $[a]$ −26.5 (*c* 1, $CHCl_3$); ν_{max}(film) 1641m and 1605m cm^{-1}; ^{1}H NMR δ 1.17 (d, *J* 7.0, 3H), 2.31–2.47 (m, 1H), 2.70 (dd, *J* 7.9 and 10.4, 1H), 2.82 (dd, *J* 4.6 and 10.4, 1H), 3.26 (s, 3H), 3.23–3.30 (m, 1H), 5.02–5.06 (m, 1H), 5.09–5.12 (m, 1H), 5.81–5.99 (m, 1H) and 7.21–7.31 (m, 5H); ^{13}C NMR δ 15.2, 37.9, 40.9, 58.4, 86.5, 114.6, 126.0, 128.3, 129.4, 139.8 and 141.2; *m/z* (CI) 191 (M^+ + 1, 100%), 135 (70) and 91 (40).

(2*E*,4*S*,5*S*)-Ethyl 5-methoxy-2,4-dimethyl-6-phenylhex-2-enoate *syn*-16

O_3 in O_2 was bubbled through a solution of alkene **14** (6.0 g, 31.6 mmol) in CH_2Cl_2 (200 ml) at −78 °C. The clear solution turned blue after *ca*. 90 min. The solution was degassed with N_2 for 5 min, triphenylphosphine (9.11 g, 34.8 mmol) was added, and the reaction mixture was allowed to warm to rt and was stirred for 2 h. While routinely this CH_2Cl_2 solution of aldehyde **10** was used directly in the next reaction, on occasions the solution was concentrated *in vacuo* to give neat aldehyde **10**, whose spectra agreed with those previously reported.[8c,g,j] (Ethoxycarbonylethylidene)triphenylphosphorane **15** (22.7 g, 63.2 mmol) was added and the mixture was heated to reflux for 48 h. The reaction mixture was allowed to cool to ambient temperature and was concentrated *in vacuo*. The residues was dissolved in CH_2Cl_2 (10 ml) and applied to the top of a silica gel pad and eluted with 50% Et_2O in petroleum spirit (500 ml). The filtrate was concentrated *in vacuo* and purified by short-path distillation (150 °C at 0.05 mmHg) to give a clear oil (7.3 g). ^{1}H NMR analysis indicated the products of the reaction were the *ester* ***syn*-16** (diagnostic peak 3-H, δ 6.69, dq, *J* 1.5 and 10.2)

** ADDA·TFA was prepared by Dr Raghu Samy of Professor Peter Toogood's laboratory at the Department of Chemistry at the University of Michigan. Peter Toogood is currently at Parke Davis Pharmaceutical Research, Ann Arbor, Michigan.

and the corresponding 4*R* epimer ***anti*-16** (diagnostic peak 3-H, δ 6.81, dq, *J* 1.5 and 9.9) in a ratio of 95:5. No evidence of the (2*Z*,4*S*,5*S*)-(diagnostic peak 3-H, δ 5.96, dq, *J* 1.5 and 9.7) or (2*Z*,4*R*,5*S*)-(diagnostic peak 3-H, δ 5.86, dq, *J* 1.5 and 9.9) isomers was detected. The spectral data for the *ester* ***syn*-16** agreed with those reported previously[8c,e] and the product from this reaction was used without additional purification.

(2*E*,4*S*,5*S*)-5-Methoxy-2,4-dimethyl-6-phenylhex-2-en-1-ol *syn*-9

$LiAlH_4$ (1.0 M in Et_2O; 39.6 ml, 39.6 mmol) was added dropwise to a solution of the esters ***syn*-16** and ***anti*-16** (7.3 g, 26.4 mmol) in Et_2O (200 ml) at −78 °C. The reaction mixture was stirred at this temperature for 1 h after which time the solid CO_2–acetone-bath was replaced with an ice-bath and the mixture was stirred for a further 1 h. TLC analysis [silica gel; 25% Et_2O in petroleum spirit] indicated no starting material (R_f 0.8) remained. $Na_2SO_4 \cdot 10H_2O$ was added while the internal temperature was maintained below +10 °C. Aq. NaOH (1 ml; 30%) was added and the mixture was stirred for 30 min. Anhydrous $NaSO_4$ was added, the reaction mixture was filtered, and the filtrate was concentrated *in vacuo* to give the alcohol ***syn*-9**, containing 5% of ***anti*-9**, as a clear oil (6.2 g, 100%). The spectral data for the alcohol ***syn*-9** agreed with those reported previously[8c,e] and the product from this reaction was used without additional purification.

(2*E*,4*S*,5*S*)-5-Methoxy-2,4-dimethyl-6-phenylhex-2-enyl-(triphenyl)phosphonium bromide 7a

CBr_4 (16.9 g, 51 mmol) in CH_3CN (100 ml) was added dropwise to a degassed solution of the mixture of alcohols ***syn*-9** and ***anti*-9** prepared above (6.2 g, 26.5 mmol) and PPh_3 (13.4, 51 mmol) in CH_3CN (200 ml) at rt in the dark. Cooling of the reaction mixture to 0 °C during the addition of the CBr_4 solution resulted in precipitation of PPh_3. While reactions conducted without degassing of the mixture and exposed to light gave substantial bromide, some oxidation of the alcohol to the corresponding aldehyde occurred. The mixture was stirred overnight at rt and was then concentrated *in vacuo*. Column chromatography (silica gel; petroleum spirit) gave the desired bromide containing ~30% $CHBr_3$. Short-path distillation (130 °C at 0.07 mmHg) gave the (2*E*,4*S*,5*S*)-1-bromo-2,4-dimethyl-5-methoxy-6-phenylhex-2-ene ***syn*-17**, containing 5% of ***anti*-17**, as clear oil (5.4 g, 68%) whose spectral data agreed with those previously reported for this compound.[8c] The mixture of bromides was treated with PPh_3 according to the general procedure outlined in ref. 8*c* to give the *phosphonium salt* **7a** as a solid which could not be purified by recrystallisation and was used directly in subsequent coupling reactions. ^{1}H NMR (major ***syn*-7a** isomer only) δ 0.80 (d, *J* 7.0, 3H), 1.39 (dd, *J* 1.3 and 3.3, 3H), 2.15–2.26 (m, 1H), 2.44–2.53 (m, 2H), 3.02–3.11 (m, 1H), 3.12 (s, 3H), 4.44–4.58 (m, 1H), 4.79–4.93 (m, 1H), 5.31–5.39 (m, 1H), 7.03–7.34 (m) and 7.61–7.94 (m, ArH over-integrates due to small amounts of triphenylphosphine).

(2*E*,4*S*,5*S*)-1-Diphenylphosphinoyl-5-methoxy-2,4-dimethyl-6-phenylhex-2-ene *syn*-7b

The mixture of bromides ***syn*-17** and ***anti*-17** prepared using the method described above (5.4 g, 18.0 mmol) was dissolved in THF (50 ml) and treated with a solution of ethyl diphenylphosphinite (4.2 g, 18.2 mmol) in THF (50 ml). The solution was degassed with Ar and heated to reflux overnight. Concentration of the reaction mixture *in vacuo* and recrystallisation of the residue from 50% Et_2O in petroleum spirit (60 ml) gave the *phosphine oxide* ***syn*-7b** (5.6 g, 51% from the 95:5 mixture of alcohols ***syn*-9** and ***anti*-9**), mp 87–88 °C (Found: C, 77.2; H, 7.5. $C_{27}H_{31}O_2P$ requires C, 77.5; H, 7.5%); [*a*] −10.0 (*c* 1, $CHCl_3$); ν_{max}(KBr) 2948s, 1436s, 1184s, 1105s, 734s, 699s and 555s cm^{-1}; ^{1}H NMR δ 0.80 (d, *J* 6.8, 3H), 1.65 (dd, *J* 1.3 and 2.7, 1H), 2.29–2.49 (m, 2H), 2.62 (dd, *J* 4.6 and 13.9, 2H), 2.93–3.03 (m, 1H), 3.05–3.14 (m, 2H), 3.10 (s, 3H), 4.97–5.05 (m, 1H), 6.98–7.34 (m, 5H), 7.31–7.62 (m, 6H) and 7.66–8.08 (m, 4H); ^{13}C NMR δ 16.0 (*J* 3.6), 18.4, 36.5 (d, *J* 2.2), 37.8, 41.0 (d, *J* 68), 58.3, 86.5 (d, *J* 2.1), 125.7 (d, *J* 10.2), 125.7, 127.9, 128.4 (dd, *J* 5.8 and 11.6), 129.3, 130.8–131.0 (m), 131.4–131.6 (m), 132.0 (d, *J* 11.4) and 133.8 (d, *J* 10.1); *m*/*z* (APCI) 419 ($M^+ + 1$, 100%) and 117 (30).

2-{[(2*E*,4*S*,5*S*)-5-Methoxy-2,4-dimethyl-6-phenylhex-2-enyl]-sulfonyl}benzothiazole *syn*-7c

The alcohol ***syn*-9** was separated from alcohol ***anti*-9** after conversion to the TBDMS ethers ***syn*-18** and ***anti*-18** according to ref. 8*e*. DEAD (4.25 ml, 27.0 mmol) was added dropwise to a solution of the alcohol ***syn*-9** (5.75 g, 24.6 mmol), BtSH (4.51 g, 27.0 mmol) and triphenylphosphine (7.08 g, 27.0 mmol) in THF (300 ml) at −10 °C. The reaction mixture was stirred for 1 h at this temperature and concentrated *in vacuo*. Column chromatography (silica gel; 30% Et_2O in petroleum spirit) gave 2-{[(2*E*,4*S*,5*S*)-5-methoxy-2,4-dimethyl-6-phenylhex-2-enyl]-thio}benzothiazole as clear oil (9.4 g, 100%), [*a*] −43.1 (*c* 1, $CHCl_3$); ν_{max}(film): 2932s, 2826s, 1603w, 1459s and 1428 cm^{-1}; ^{1}H NMR δ 0.97 (d, *J* 6.8, 3H), 1.67 (d, *J* 1.3, 1H), 2.35–2.53 (m, 1H), 2.57 (dd, *J* 7.4 and 13.9, 1H), 2.73 (dd, *J* 4.6 and 13.9, 1H), 3.07–3.15 (m, 1H), 3.17 (s, 3H), 3.99 (ABX, *J* 0.9 and 13.3, 2H), 5.52 (dq, *J* 1.2 and 9.7, 1H), 7.06–7.45 (m, 7H), 7.71–7.76 (m, 1H) and 7.87–7.92 (m, 1H). ^{13}C NMR δ 15.3, 15.8, 36.5, 37.7, 42.8, 58.3, 86.4, 120.6, 121.2, 123.9, 125.6, 125.7, 127.8, 129.0, 129.1, 133.2, 134.9, 138.9, 152.8 and 166.4; *m*/*z* (CI) 384 ($M^+ + 1$, 65%), 185 (30), 168 (95), 135 (100) and 134 (40). This material was oxidised directly using one of the following procedures.

Method A. Oxone® (3.34 g, 10.98 mmol of $KHSO_5$) in water (40 ml) was added dropwise to a solution of the sulfide (1.40 g, 3.66 mmol) in MeOH (40 ml) with the internal temperature kept below +10 °C. The cooling bath was removed and the mixture was stirred at rt and monitored by TLC. The sulfide (R_f 0.9; silica gel; 30% Et_2O in petroleum spirit) was converted to the more polar (R_f 0.3) sulfoxide within 1 h, which was itself oxidised more slowly to the desired sulfone (R_f 0.45) after 6 h at rt. The mixture was diluted with water, extracted with $CHCl_3$ (3 × 100 ml) and the organic extracts were dried ($MgSO_4$), filtered, and concentrated *in vacuo* to give a clear oil. Purification by column chromatography (silica gel; 30–70% Et_2O in petroleum spirit) gave the *sulfone* **7c** (1.10 g, 72%) as a solid, mp 88.5–89 °C (Found: C, 63.5; H, 6.2; N, 3.5. $C_{22}H_{25}NO_3S$ requires C, 63.6; H, 6.1; N, 3.4%); [*a*] −25.1 (*c* 1, $CHCl_3$); ν_{max}(KBr) 2929s, 2894s, 1661s and 1474s cm^{-1}; ^{1}H NMR δ 0.80 (d, *J* 7.0, 3H), 1.65 (d, *J* 1.3, 1H), 2.34–2.59 (m, 3H), 2.88–2.96 (m, 1H), 3.02 (s, 3H), 4.16 (s, 2H), 5.26 (d, *J* 9.9, 1H), 7.00–7.26 (m, 5H), 7.48–7.64 (m, 2H), 7.91–7.96 (m, 1H) and 8.18–8.23 (m, 1H). ^{13}C NMR δ 14.9, 16.6, 36.3, 37.4, 58.0, 64.1, 85.7, 121.6, 121.9, 125.0, 125.7, 127.3, 127.6, 127.8, 128.9, 136.5, 138.6, 140.3, 152.3 and 165.2; *m*/*z* (APCI) 416 ($M^+ + 1$, 100%), 384 (50) and 136 (45) [Found: *m*/*z* 416.1391. $C_{22}H_{26}NO_3S$ ($M + 1$) requires *m*/*z*, 416.1428].

Method B. Ammonium molybdate(VI) tetrahydrate (2.16 g, 1.75 mmol) in H_2O_2 (30% in H_2O; 3.2 ml, 28 mmol) was added to a solution of the sulfide (2.68 g, 7.0 mmol) in EtOH (50 ml) at 0 °C. The cooling bath was removed and the reaction was followed by TLC (see method A). The mixture was diluted with Et_2O (200 ml) and water (200 ml). The organic phase was separated, washed with brine (200 ml), dried ($MgSO_4$), and filtered, and the filtrate was concentrated *in vacuo* to give a clear oil. Purification as described in method A gave the sulfone **7c** as a solid (2.18 g, 75%).

Dibenzyl *N*-(*tert*-butyldimethylsilyl)-D-aspartate 20

NEt_3 (11.0 ml, 79.1 mmol) was added dropwise over a period of

1 h to a solution of TBDMSCl (5.7 g, 37.8 mmol), D-aspartic acid dibenzyl ester toluene-*p*-sulfonate[17] **19** (16.2 g, 34.4 mmol) and DMAP (207 mg, 1.7 mmol) in CH_2Cl_2 (200 ml) under argon. The mixture was stirred for 16 h at rt and was then poured into saturated aq. NH_4Cl (200 ml), the organic layer was separated, washed (saturated aq. $NaHCO_3$), dried (Na_2SO_4), and evaporated *in vacuo* to give the *diester* **20** as an oil (14.4 g) which was used immediately in the next reaction. The ^{1}H NMR data agreed with those reported for the opposite enantiomer.[4f]

(2*R*)-Benzyl *N*-(*tert*-butyldimethylsilyl)-4-oxoazetidine-2-carboxylate 22

A solution of compound **20** (14.4 g) in dry Et_2O was cooled to 0 °C in an ice/salt-bath under argon. ^{t}BuMgCl (20.0 ml, 40.0 mmol; 2 M in Et_2O) was added dropwise over a period of 40 min *via* a syringe pump. The mixture was kept at 0 °C for a further 1 h, the cooling bath was removed, and the solution was allowed to warm to rt and was stirred for 16 h. The mixture was recooled to 0 °C and saturated aq. NH_4Cl (20 ml) was added dropwise. The mixture was diluted with water (300 ml), the organic layer was separated, and the aqueous layer was extracted with Et_2O (2 × 200 ml). The combined organics were dried ($MgSO_4$) and the solvent was removed *in vacuo* to give a yellow oil (12.9 g) containing an equimolar amount of the *lactam* **22** and benzyl alcohol and which was used in the next reaction without further purification. The ^{1}H NMR spectrum for the *lactam* **22** agreed with that reported for the opposite enantiomer.[4f]

(4*R*)-*N*-(*tert*-Butyldimethylsilyl)-4-(hydroxymethyl)azetidin-2-one 23

A suspension of sodium borohydride (3.08 g, 81.5 mmol) in THF (150 ml) and a solution of lithium bromide (7.08 g, 81.5 mmol) in water (45 ml) were placed in the same dropping funnel and added dropwise over a period of 40 min to a solution of lactam **22** (12.9 crude, ~9.6 g lactam, ~30 mmol) in THF (150 ml) at such a rate that the internal temperature did not rise above 28 °C and the mixture was stirred for a further 40 min at rt. Saturated aq. NH_4Cl (75 ml) was added dropwise, the organic layer was separated, and the aqueous layer was extracted with ethyl acetate (2 × 150 ml). The combined organic extracts were dried ($MgSO_4$), and the solvent was removed *in vacuo* to give a yellow oil. Purification by column chromatography (silica gel; 30% ethyl acetate in petroleum spirit to 100% ethyl acetate) give the *alcohol* **23** (4.6 g, 62% from **19**) as an oil which solidified upon storage to give a low melting solid, [*a*] +30.2 (*c* 1, $CHCl_3$) {lit.,[18] [(4*S*)-enantiomer] $[a]_D$ −32.1 (*c* 1, $CHCl_3$) lit.,[6b] [(4*S*)-enantiomer] $[a]_D$ −31.5 (*c* 2.7, CH_2Cl_2)}. The spectral data for this compound agreed with those reported for the racemate[4n] and opposite enantiomer.[18]

(3*S*,4*R*)-*N*-(*tert*-Butyldimethylsilyl)-4-hydroxymethyl-3-methylazetidin-2-one 25

Method A (LDA). A solution of compound **23** (650 mg, 3.0 mmol) in THF (20 ml) was added dropwise over a period of 20 min to a freshly prepared solution of LDA (6.7 mmol) in THF (10 ml) at −78 °C. The mixture was stirred at this temperature for 30 min, then methyl iodide (0.62 ml, 10.0 mmol) was added dropwise. The mixture was stirred for a further 2 h at −78 °C, MeOH (1.0 ml) was added dropwise followed by saturated aq. NH_4Cl (14 ml) and the mixture was allowed to warm to rt. The mixture was extracted with Et_2O (3 × 30 ml), the extract was dried ($MgSO_4$) and the solvent was removed *in vacuo* to give an oil. Column chromatography (silica gel; 50% ethyl acetate in petroleum spirit) gave the *alcohol* **25** (456 mg, 66%) as a solid, mp 63.5–65 °C (Found: C, 57.5; H, 10.1; N, 6.1. $C_{11}H_{23}NO_2Si$ requires C, 57.6; H, 10.1; N, 6.1%); [*a*] +2.6 (*c* 1, $CHCl_3$); ν_{max}(KBr) 3384s and 1702s cm^{-1}; ^{1}H NMR δ 0.25 (s, 3H), 0.26 (s, 3H), 0.96 (s, 9H), 1.31 (d, *J* 7.5, 3H), 1.70 [br s (exch), 1H], 3.05 (dq, *J* 2.4 and 7.5, 1H), 3.27 (ddd, *J* 2.4, 4.2 and 5.3, 1H), 3.68 (dd, *J* 5.3 and 11.5, 1H) and 3.76 (dd, *J* 4.2 and 11.5, 1H); ^{13}C NMR δ −5.3, −5.1, 14.0, 18.8, 26.5, 49.1, 59.1, 64.5 and 177.2; *m*/*z* (CI) 230 (M^+ + 1, 100%), 214 (15) and 174 (20).

Method B (*n*-BuLi). *n*-BuLi (1.2 M in hexane; 27.5 ml, 33.0 mmol) was added dropwise during 40 min to a solution of (4*R*)-*N*-(*tert*-butyldimethylsilyl)-4-(hydroxymethyl)azetidin-2-one **23** (3.50 g, 16.3 mmol) in THF (200 ml) at −78 °C. The mixture was stirred at this temperature for 45 min then methyl iodide (3.4 ml, 54.6 mmol) was added dropwise over a period of 15 min. The mixture was stirred for a further 2 h at −78 °C and then was worked up as described above. Column chromatography (silica gel; 45% ethyl acetate in petroleum spirit) gave the *alcohol* **25** (1.97 g, 53%) in addition to ~5% of (3*S*,4*R*)-4-(*tert*-butyldimethylsiloxymethyl)-3-methylazetidin-2-one **26** (Found: C, 57.8; H, 10.2; N, 5.9%) [*a*] −44.8 (*c* 1, $CHCl_3$); ν_{max}(KBr) 3199s and 1755s cm^{-1}; ^{1}H NMR δ −0.02 (s, 6H), 0.81 (s, 9H), 1.22 (d, *J* 7.5, 3H), 2.80 (ddq, *J* 1.0, 2.0 and 7.5, 1H), 3.27 (ddd, *J* 2.0, 4.9 and 5.8, 1H), 3.57 (dd, *J* 5.8 and 10.6, 1H), 3.67 (dd, *J* 4.9 and 10.6, 1H) and 6.50 (br s, 1H); ^{13}C NMR δ −5.2, 13.1, 18.5, 26.0, 48.3, 57.5, 65.2 and 171.9; *m*/*z* (CI) 230 (M^+ + 1, 100%), 185 (10), 158 (15) and 116 (15) [Found: M^+ + 1, 230.1587. $C_{11}H_{24}NO_2Si$ (*M* + 1) requires *m*/*z* 230.1598].

(2*R*,3*S*)-*N*-(*tert*-Butyldimethylsilyl)-3-methyl-4-oxoazetidine-2-carbaldehyde 8a

Oxalyl dichloride (0.98 ml, 11.2 mmol) as a solution in CH_2Cl_2 (46.0 ml) was cooled to −78 °C, DMSO (1.49 ml, 21.05 mmol) as a solution in CH_2Cl_2 (6.0 ml) was added dropwise over a period of 10 min and the mixture was stirred for a further 15 min. A solution of compound **25** (1.90 g, 8.3 mmol) in CH_2Cl_2 (23.0 ml) was then added dropwise during 10 min and the mixture was stirred for 30 min before NEt_3 (5.35 ml, 38.4 mmol) was added. The mixture was stirred at −78 °C for 15 min then was allowed to warm to rt over a period of 1 h. Saturated aq. NH_4Cl (30 ml) was added and the mixture was poured into Et_2O (250 ml) and water (100 ml) and the organic layer was separated. The aqueous layer was extracted with Et_2O (3 × 80 ml) and the combined organics were washed with saturated aq. sodium chloride (2 × 150 ml), dried (Na_2SO_4), and evaporated *in vacuo* to give the *aldehyde* **8a** as a viscous oil (1.70 g, 90%), [*a*] +15.2 (*c* 1, $CHCl_3$); ν_{max}(film) 1741 (br s cm^{-1}); ^{1}H NMR δ 0.13 (s, 3H), 0.29 (s, 3H), 0.96 (s, 9H), 1.42 (d, *J* 7.5, 3H), 3.24 (dq, *J* 2.7 and 7.5, 1H), 3.60 (dd, *J* 2.7 and 4.4, 1H) and 9.61 (d, *J* 4.4, 1H); ^{13}C NMR δ −6.1, −6.0, 13.2, 18.1, 25.8, 49.4, 62.6, 188.4 and 199.0; *m*/*z* (CI) 228 (M^+ + 1, 100%), 209 (35), 172 (30), 158 (15), 133 (20), 114 (40) and 71 (22) [Found: M^+ + 1, 228.1433. $C_{11}H_{22}NO_2Si$ (*M* + 1) requires *m*/*z* 228.1446].

General procedure for coupling compounds 7a–c with aldehyde 8a

Base (1 equiv.) was added dropwise to a solution of a compound **7a**–**c** in THF (~0.1 mM) at −78 °C and the mixture was stirred for 30 min. A solution of the aldehyde **8a** (1.1 equiv.) in THF (~0.2 mM) was added dropwise at −78 °C and the reaction mixture was stirred at this temperature before being allowed to warm to rt during 2 h. The reaction was quenched with saturated aq. NH_4Cl (20 ml) and the mixture was diluted with Et_2O (40 ml). The organic phase was separated and the aqueous phase was extracted with Et_2O (20 ml). The combined organic extracts were dried ($MgSO_4$), filtered, and concentrated *in vacuo* to give a yellow oil. Purification by column chromatography (silica gel; 50% Et_2O in petroleum spirit) gave the *lactam* **6a** as a clear oil. For reaction involving substrates **7a** and **7b**, material obtained in this way was of sufficient purity for characterisation. For reaction products from sulfone **7c**, final purification was effected after treatment with KF (see below).

(3*S*,4*S*)-*N*-[*tert*-Butyldimethylsilyl]-4-[(1*E*,3*E*,5*S*,6*S*)-6-methoxy-3,5-dimethyl-7-phenylhepta-1,3-dienyl]-3-methylazetidin-2-one 6a. ν_{max}(film) 1747s cm^{-1}; ^1H NMR δ 1.05 (d, *J* 6.8, 3H), 1.30 (d, *J* 7.5, 3H), 1.63 (d, *J* 1.1, 3H), 2.56–2.84 (m, 3H), 2.92 (dd, *J* 2.6 and 7.5, 1H), 3.15–3.20 (m, 1H), 3.23 (s, 3H), 3.62 (dd, *J* 2.6 and 9.1, 1H), 5.40 (d, *J* 9.9, 1H), 5.51 (dd, *J* 9.1 and 15.5, 1H), 6.20 (d, *J* 15.5, 1H) and 7.16–7.26 (m, 5H). ^{13}C NMR δ −5.92, −5.70, 12.4, 12.9, 15.8, 18.0, 25.9, 36.2, 37.8, 53.4, 58.3, 60.2, 86.6, 125.6, 127.3, 127.8, 129.0, 132.0, 136.0, 137.0, 139.0 and 176.0; *m*/*z* (CI) 428 ($M^+ + 1$, 100%), 412 (25), 294 (20) and 135 (40) [Found: $M^+ + 1$, 428.2989. $C_{26}H_{42}NO_2Si$ (*M* + 1) requires *m*/*z* 428.2993].

Diagnostic peaks for *E*,*Z*-diene: ^1H NMR δ 4.16 (dd, *J* 2.6 and 9.9, 1H) and 5.97 (d, *J* 11.3, 1H).

(3*S*,4*S*)-4-[(1*E*,3*E*,5*S*,6*S*)-6-Methoxy-3,5-dimethyl-7-phenylhepta-1,3-dienyl]-3-methylazetidin-2-one 31

KF (46.5 mg, 0.8 mmol) as a mixture in MeOH (6 ml) was added rapidly to a solution of the *N*-silyl lactam **6a** (280 mg, 0.7 mmol) in MeOH (15 ml) at 0 °C. The mixture was stirred at this temperature and monitored by TLC. After 4.5 h no starting material was present. Glacial acetic acid (40 μl) was added and the mixture was stirred for a further 10 min before being concentrated and the residue was purified by column chromatography (silica gel; 30–70% Et_2O in petroleum spirit) to give the *lactam* **31** as an oil (45% yield from sulfone **7c**, see text), ν_{max}(film) 3202m and 1755s cm^{-1}; ^1H NMR δ 1.04 (d, *J* 6.8, 3H), 1.34 (d, *J* 7.5, 3H), 1.65 (d, *J* 1.3, 1H), 2.56–2.96 (m, 4H), 3.21–3.24 (m, 1H), 3.23 (s, 3H), 3.78 [(after D_2O exch.) dd, *J* 2.6 and 8.0, 1H], 5.43 (d, *J* 10.4, 1H), 5.58 (dd, *J* 8.0 and 15.5, 1H), 5.90 [br s (D_2O exch.), 1H], 6.27 (d, *J* 15.5, 1H) and 7.11–7.31 (m, 5H); ^{13}C NMR δ 12.3, 15.8, 29.9, 36.2, 37.8, 53.5, 57.9, 58.2, 86.5, 125.5, 125.7, 127.8, 129.0, 131.9, 136.5, 137.0, 138.9 and 171.0; *m*/*z* (APCI) 314 ($M^+ + 1$, 100%), 180 (35) and 117 (60) [Found: $M^+ + 1$, 314.2103. $C_{22}H_{28}NO_2$ (*M* + 1) requires *m*/*z* 314.2086].

Diagnostic peaks for *E*,*Z*-diene: ^1H NMR δ 4.22 [ddd, *J* 0.9, 2.2 and 9.3; (after D_2O exch.) dd, *J* 2.2 and 9.3, 1H] and [6.01 (d, *J* 11.1, 1H)].

(3*S*,4*S*)-*N*-[*tert*-Butoxycarbonyl]-4-[(1*E*,3*E*,5*S*,6*S*)-6-methoxy-3,5-dimethyl-7-phenylhepta-1,3-dienyl]-3-methylazetidin-2-one 4

NEt_3 (0.19 ml, 1.4 mmol), a solution of $(Boc)_2O$ (598 mg, 2.7 mmol) in CH_2Cl_2 (10 ml), and DMAP (167 mg, 1.4 mmol) were added to a solution of lactam **31** (430 mg, 1.4 mmol) in CH_2Cl_2 (10 ml). The mixture was stirred overnight at rt and concentrated. The ^1H NMR spectrum of the crude product (770 mg) showed only DMAP in addition to the *lactam* **4** (90–95% yield based on added DMAP). This material was either treated with lithium hydroxide (see below) to form *N*-Boc-ADDA or purified by column chromatography (silica gel; 30% Et_2O in petroleum spirit) to give the lactam **4** as an oil (340 mg, 60%), [*a*] −11.6 (*c* 1, $CDCl_3$); ν_{max}(film) 1811s and 1718s cm^{-1}; ^1H NMR δ 1.02 (d, *J* 6.8, 3H), 1.34 (d, *J* 7.5, 3H), 1.47 (s, 9H), 1.64 (d, *J* 1.3, 1H), 2.56–2.89 (m, 3H), 2.95 (dq, *J* 2.9 and 7.5, 1H), 3.15–3.22 (m, 1H), 3.22 (s, 3H), 4.02 (dd, *J* 2.6 and 8.3, 1H), 5.44 (d, *J* 12.0, 1H), 5.65 (dd, *J* 8.3 and 15.5, 1H), 6.33 (d, *J* 15.5, 1H) and 7.16–7.29 (m, 5H); ^{13}C NMR δ 11.3, 12.3, 16.1, 28.0, 36.6, 38.1, 51.6, 58.6, 61.4, 82.9, 86.8, 123.0, 126.0, 128.2, 129.4, 132.2, 137.2, 139.2, 147.9 and 168.4 (quat. aromatic not observed); *m*/*z* (APCI) 413 ($M^+ + 1$, 100%), 313 (50), 219 (60), 166 (60) and 150 (80).

Diagnostic peaks for *E*,*Z*-diene: ^1H NMR δ 4.49 (dd, *J* 2.9 and 9.7, 1H) and 6.09 (d, *J* 11.3, 1H).

{(2*S*,3*S*,4*E*,6*E*,8*S*,9*S*)-3-(*tert*-Butoxycarbonylamino)-9-methoxy-2,6,8-trimethyl-10-phenyldeca-4,6-dienoyl}glycine methyl ester 5 (X = H, *n* = 0, R = Me)

NaN_3 (26 mg, 0.4 mmol) was added to a mixture of *N*-Boc lactam **4** (70 mg, 0.17 mmol), glycine methyl ester hydrochloride (50 mg, 0.4 mmol) and NEt_3 (53 μl, 0.38 mmol) in DMF (3 ml). The mixture was stirred at rt for 5½ days, diluted with Et_2O, washed successively with water (3 × 25 ml) and aq. citric acid (10%; 2 × 25 ml), dried ($MgSO_4$), and filtered, and the filtrate was concentrated *in vacuo* to give a slightly yellow oil. Column chromatography (silica gel; 80% Et_2O in petroleum spirit) gave the starting material (7 mg, 10% recovery) in addition to the *dipeptide* **5** as a waxy solid (65 mg, 76%) (Found: C, 66.7; H, 8.7; N, 5.3. $C_{28}H_{42}N_2O_6$ requires C, 66.9; H, 8.4; N, 5.6%); [*a*] −13.0 (*c* 1.0, $CHCl_3$); ν_{max}(KBr) 3310, 1762, 1688 and 1665 cm^{-1}; ^1H NMR δ 1.02 (d, *J* 6.8, 3H), 1.24 (d, *J* 6.9, 3H), 1.44 (s, 9H), 1.62 (d, *J* 1.1, 3H), 2.56–2.70 (m, 3H), 2.81 (dd, *J* 4.5 and 13.8, 1H), 3.15–3.24 (m, 1H), 3.22 (s, 3H), 3.74 (s, 3H), 3.95–3.99 (m, 2H), 4.22 (m, 1H), 5.38 (d, *J* 9.9, 1H), 5.50 (dd, *J* 6.9 and 15.6, 1H), 5.80 (m, 1H), 6.20 (d, *J* 15.6, 1H), 6.34 (m, 1H) and 7.13–7.31 (m, 5H); ^{13}C NMR δ 12.7, 15.3, 16.3, 28.4, 36.5, 38.1, 41.0, 44.7, 52.3, 55.6, 58.5, 79.1, 86.9, 125.8, 125.9, 128.1, 129.3, 132.6, 135.6, 136.2, 139.4, 155.9, 170.1 and 175.1; *m*/*z* (CI) 503 (M^+, 10%), 447 (20), 403 (45), 386 (25), 252 (100) and 135 (15) [Found $M^+ + 1$, 504.3191. $C_{28}H_{43}N_2O_6$ (*M* + 1) requires *m*/*z* 504.3199].

Reaction of samples of the *N*-Boc lactam **4** containing the 4*Z* isomer gave the corresponding dipeptide {(2*S*,3*S*,4*Z*,6*E*,8*S*,9*S*)-3-(*tert-butoxycarbonylamino*)-9-*methoxy*-2,6,8-*trimethyl*-10-*phenyldeca*-4,6-*dienoyl*}*glycine methyl ester* **5** [*a*] −31.5 (*c* 0.66, $CDCl_3$); ^1H NMR δ 1.05 (d, *J* 6.8, 3H), 1.20 (d, *J* 7.1, 3H), 1.42 (s, 9H), 1.72 (d, *J* 1.1, 3H), 2.44–2.65 (m, 2H), 2.72 (dd, *J* 7.7 and 13.9, 1H), 2.86 (dd, *J* 4.6 and 13.9, 1H), 3.21–3.24 (m, 1H), 3.23 (s, 3H), 3.75 (s, 3H), 3.98 [d, *J* 5.3, 3H (D_2O exch.)], 3.98 (s, 3H), 4.73 (m, 1H), 5.26 (dd, *J* 9.7 and 11.7, 1H), 5.36 (d, *J* 9.7, 1H), 5.56 [m, 1H (D_2O exch.)], 5.92 (d, *J* 11.7, 1H), 6.15 [m, 1H (D_2 exch.)] and 7.18–7.27 (m, 5H); ^{13}C NMR δ 15.2, 16.3, 16.6, 28.4, 36.4, 38.1, 41.0, 45.5, 51.2, 52.4, 58.6, 79.0, 86.9, 125.9, 128.2, 129.4, 132.0, 134.6, 134.7, 139.5, 155.5, 170.2 and 174.9; *m*/*z* (CI) 503 (M^+, 15%), 447 (15), 403 (100) and 252 (75) [Found: $M^+ + 1$, 504.3195. $C_{28}H_{43}N_2O_6$ (*M* + 1) requires *m*/*z* 504.3199].

(2*S*,3*S*,4*E*,6*E*,8*S*,9*S*)-3-(*tert*-Butoxycarbonylamino)-9-methoxy-2,6,8-trimethyl-10-phenyldeca-4,6-dienoic acid *N*-Boc-ADDA

The crude mixture of *N*-Boc lactam **4** and DMAP prepared above was dissolved in THF (21 ml) and treated dropwise with aq. LiOH (4.1 ml; 1 M) at rt. The mixture was stirred at rt overnight. The THF was removed *in vacuo*, water (10 ml) was added and the solution acidified to pH 3.5–4.0 with 10% acetic acid, before being extracted with Et_2O (3 × 30 ml). The combined organics were dried ($MgSO_4$) and filtered, and the filtrate was concentrated *in vacuo* to give a yellow oil. Column chromatography (silica gel; 40% EtOAc in petroleum spirit) gave *N*-Boc-ADDA as an oil (510 mg, 86% yield for the two steps from lactam **31**). The spectral data for this compound agreed with those previously reported.[8c,g,i,j]

(2*S*,3*S*,4*E*,6*E*,8*S*,9*S*)-3-Amino-9-methoxy-2,6,8-trimethyl-10-phenyldeca-4,6-dienoic acid hydrochloride ADDA·HCl

A solution of *N*-Boc-ADDA (36 mg, 0.09 mmol) in EtOAc (1.5 ml) was treated with a 1.5 ml aliquot of a saturated solution of HCl in EtOAc. The mixture was stirred at rt for 4 h before being concentrated *in vacuo* to give ADDA·HCl as an oil (32 mg, 100%) whose spectra agreed with those reported perviously[8e] for the free amino acid: ^1H NMR (d_4-MeOH) δ 1.19 (d, *J* 6.8, 3H), 1.40 (d, *J* 7.1, 3H), 1.81 (s, 3H), 2.78–3.02 (m, 4H), 3.36–3.45 (m, 1H), 3.40 (s, 3H), 4.15 (m, 1H), 5.61–5.77 (m, 2H), 6.64 (d, *J* 15.3, 1H) and 7.28–7.41 (m, 5H); ^{13}C NMR (d_4-MeOH) δ 11.2, 13.0, 14.8, 35.7, 36.1, 37.3, 55.5, 57.2, 86.6, 119.0, 125.6, 127.7, 129.0, 131.8, 138.6, 138.9, 141.9 and 174.9.

(2*S*,3*S*,4*E*,6*E*,8*S*,9*S*)-3-Amino-9-methoxy-2,6,8-trimethyl-10-phenyldeca-4,6-dienoic acid ADDA

Method A. ADDA·HCl was dissolved in methanol and applied to a preparative RP-HPLC column (Econosil C18, I.D. 22 mm × 250 mm; flow rate 5.0 ml min^{-1}) and eluted with 6:4 methanol–water containing 5 mM ammonium formate. Collection of the eluent containing product and concentration gave free amino acid ADDA as a hygroscopic solid, [*a*] −38.9 (*c* 0.375, EtOH); ^{1}H NMR (500 MHz; d_4-MeOH) δ 1.02 (d, *J* 6.8, 3H), 1.20 (d, *J* 7.2, 3H), 1.64 (s, 3H), 2.42 (ap. t, *J* 7.2, 1H), 2.62 (m, 1H), 2.68 (dd, *J* 7.3 and 14.0, 1H), 2.80 (dd, *J* 4.8 and 14.0, 1H), 3.24 (s, 3H), 3.21–3.27 (m, 1H), 3.68 (ap. t, *J* 8.4, 1H), 5.50 (dd, *J* 8.8 and 15.6, 1H), 5.54 (d, *J* 9.5, 1H), 6.41 (d, *J* 15.6, 1H) and 7.14–7.19 (m) and 7.22–7.26 (m, together 5H); ^{13}C NMR (125 MHz; d_4-MeOH) δ 12.7, 16.1, 16.3, 37.7, 38.9, 44.8 br, 58.3, 58.7, 88.2, 122.7, 127.1, 129.2, 130.5, 133.5, 139.4, 140.5, 142.2 and 180.8; *m*/*z* (CI) 332 (M + H, 33%), 300 (15), 258 (10) and 135 (100).

Method B. ADDA·TFA (10 mg) was dissolved in aq. ammonia (5%; 1.0 ml) and freeze dried to give the free amino acid ADDA whose spectral details agreed with those reported above.

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